

PATENT SPECIFICATION

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(54) SINGLE LIQUID DOSE HOLDER

(71) We, CIBA-GEIGY A.G. a body corporate organised according to the laws of Switzerland, of 4002 Basle, Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a single liquid dose holder.

In, for example, medical or pesticidal treatment it is desired to deliver in a single application an accurate dosage. Methods are already known by which liquids and also powders may be dispensed in specific amounts from an aerosol dispensing container in which the liquids or powders are mixed with a gaseous propellant, such as highly halogenated lower alkanes (e.g. Freon — registered Trade Mark), butane/propane mixtures, carbon dioxide and/or nitrogen, by the opening of a dosing valve mounted on the container. A suitable dosing valve is described in the German Patent Specification No. 1 149 308 (published 25.5.1963).

Rubber balls and the like serving to produce a short puff of compressed air have also been used as propellant sources, e.g. in the device described in the U.S. Patent Specification No. 2 519 555 concerning a dispenser for dispensing pulverulent medicaments.

With these known devices, however, there is difficulty in obtaining an accurate dosage, particularly in the case of very small amounts extending, for example, down to a few milligrams, either because of the fact that the design of correspondingly small dosing valves with correspondingly accurate dimensioning and low tolerances is too complicated and expensive, or because of the fact that the complete removal of the stored amount of liquid from the dispenser and the transfer of this amount to the point

of application cannot be guaranteed.

The known devices fed from a propellant source operate frequently with inadequate accuracy or reliability, particularly with the dispensing of liquids in the case of which an excess of the prescribed dose would be harmful, as, for example, in the application of strictly defined single doses of highly effective medicaments; but also in other fields, e.g. in the application of accurately prescribed amounts of a liquid agent which in a larger amount would be too poisonous or too explosive, or dangerous in some other manner. This would apply with regard to the application of liquids also in the case of the dispenser for, finely dispersed powders known from the British Patent Specification No. 898, 649 of the Berger Laboratories Ltd., the design of the said dispenser being such that a specific dose of the powder is fed into the holding space of a two-part cartridge, a small aperture being provided in the end face of each of the two parts of the cartridge, the two parts, after filling, being tightly connected together, the lower part having an aperture of, e.g. 0.20 to 0.4 mm diameter, and the upper part an aperture of about 0.8 to 1.0 mm diameter. With normal handling of the cartridge, it is intended that the powder shall not escape from these apertures which, moreover, remain before use sealed by polyethylene sealing rings, but shall be blown out or sucked out on use by a stream of air. A liquid fed into this cartridge of the Berger Laboratories Ltd. can, on handling of the device, penetrate into the apertures in the end faces and thus onto the polyethylene rings or sheets sealing the apertures; and a small part of the liquid dose can be lost, or not ejected, as a result of removal of the seals.

The present invention provides a single liquid dose holder comprising a liquid dose in a container having an inlet and an out-

let, means for connecting the inlet to a propellant source and a removable or rupturable seal on the inlet, the holder being such that the liquid dose is held by capillarity in the container with a gas pocket between the said seal and the liquid dose to impede displacement of liquid from the container.

Preferably the holder also comprises a removable or rupturable seal on the outlet.

To dispense the dose, the holder is connected, on removal or rupturing of the inlet seal, to a propellant, preferably gaseous propellant, source. If necessary the outlet is opened. Then by actuation of the propellant source the liquid dose may be expelled in a single application with the greatest possible removal from the holder. Also the liquid dose may, by suitable directing of the holder, be delivered to the desired place of application. With the present holder it is possible to deliver very minute but accurately controlled doses of liquid to a desired place.

The liquid dose is held in the container by capillarity with a gas pocket between the inlet seal and the liquid dose to impede displacement of liquid from the container. This helps to ensure that the dose is not displaced from the holder during handling before use e.g. with removal of holder from its packing before use or when connecting the holder to a propellant source.

The gas pocket may be filled with air or with an inert gas e.g. nitrogen or argon. The gas pocket impedes displacement of the liquid dose on shaking of the holder.

Preferably the container of the present invention has both inlet and outlet capillary end sections such that there are such gas pockets both at the inlet and the outlet of the holder. In this way it may be ensured that none of the liquid dose is lost by flowing out or being prematurely expelled when the holder is attached to the propellant source e.g. or rupturing the inlet seal or replacing it by the valve stem of a propellant dispensing container.

Preferably the propellant source used in conjunction with the present holder has a valve such that the propellant itself is delivered in pre-determined dose units.

We have found that it is sometimes, for example if the dose is of the order of 30 to 60 mg. difficult to expel in a single application a dose from a straight tube shaped container. However if the tubing is formed longitudinally into a coil, e.g. having a double turn, the dose may be quantitatively sprayed out with only one shot of propellant. Further the holding of the dose in the holder before use is aided.

Preferably the container of the holder of the present invention consists of a length of tubing having an inside diameter capable

of providing the desired capillary effect, and bent so that a coil of at least one turn is obtained. A design of tubing which has proved very satisfactory is one in which the middle section of the tube is shaped as a coil having two or three turns. Other geometrical forms are however applicable, provided that they ensure the fixing of the desired amount of liquid in the middle section of the tubing; e.g. the centre portion of the tube may be arranged in spiral or zigzag form.

In another form the container may have inlet and outlet capillary end sections, to prevent accidental loss of liquid dose even during fairly violent handling, with the central section of the container being enlarged. For example this central section can have the form of a sphere, an ellipsoid or a double cone i.e. a circular, an oval, a rhombic, or similar axial cross-section.

The container is preferably made of synthetic material, e.g. polyethylene or polyamide (e.g. Nylon), or polytetrafluoroethylene (e.g. Teflon — registered Trade Mark), or also of glass or metal, particularly of non-corroding metals such as V₂A-steel, silver, gold, copper alloys, eloxadized aluminium, etc., the material having to be suitable for the producing of capillary tubes of suitable dimensions. For certain liquids it is also possible to use rubber hose, provided that this does not become decomposed by the liquids on prolonged storage.

For liquids having a viscosity of about 10 to 50 Centipoise (at 20°C), tubes with an inside diameter of about 0.8 to 1.5 mm and having one to two turns are especially satisfactory. Larger inside diameters are to be used in the case of a higher viscosity of the liquid to be stored, and correspondingly narrower capillaries with lower viscosity.

Liquids stored in holder according to the invention may be solutions, suspensions or emulsions of active substances, e.g. of substances having pharmaceutical or pesticidal activity, or of substances effective in technical fields. Suitable carriers and/or solvents are, in particular, oils such as sesame oil, ethyloleate and similar liquid alkyl esters of aliphatic acids, also propylene glycols of the mentioned viscosity range, and, finally, also silicone oils and suchlike, e.g. a dimethyl silicone oil having a viscosity of 25 Centipoise and a refractive index of about 1.46, both at 25°C. Aqueous solutions, suspensions or emulsions with suitable substances for increasing viscosity, e.g. sodium carboxymethyl cellulose, cellulose ethers, gel-forming natural substances such as, e.g. agar-agar, tragacanth and gelatinate, are likewise suitable.

Active substances which can be suspended, emulsified or dissolved in the above men-

tioned carriers can belong to the most diverse classes. In the case of application for inhalation, for example, medicaments such as 1-(3,4-dihydroxyphenyl)-2-isopropylamino-ethanol-sulphate for nasal administration, and active substances such as 2 - (4 - tert - butyl - 2,6 - dimethyl - 3-hydroxybenzyl) - 2 - imidazoline - hydrochloride-sulphate, can be suspended, emulsified or dissolved in the desired concentration in one of the above carriers, and the obtained preparation fed into the dispenser according to the invention, e.g.:

- 15 a) an aqueous solution consisting of, as a single dose, 0.075 mg of isoproterenol* in 35 mg of an aqueous Na-CMC solution (viscosity of 10 cps), applicable as inhalation spray (CMC = carboxymethyl cellulose);
- 20 b) a suspension consisting of, as a single dose, 0.033 mg of oxymethazoline* in 40 mg of Mygliol 812 neutral oil (triglycerides of saturated fatty acids of the chain-length C_8-C_{12}), applicable as nasal spray (*Merck Index 8th Edition).

The new device has proved particularly successful for the nasal administration (i.e. through the nasal mucous membrane) of physiologically active peptide compounds. Such peptide compounds are, e.g. insulin, growth-promoting hormone, glucagon, thyrotropin luteotropin-releasing hormone, thyrotropin-releasing hormone, vasopressin, bradykinin, etc. also hypertensin and its analogues, principally calcitonins and, in particular, peptides having MSH- and ACTH-effect.

For the above stated purposes the container should be designed to hold a dose of about 20 to 100 mg of liquid.

The holder usually employed comprises a casing consisting of an upper housing part and a base part both of which are preferably made of plastics material though they can also be made of other suitable materials such as metal or glass. The container is inserted through the base part and into the outlet opening and then the housing and base are connected by screwing, thermal welding or cementing. The desired dose of liquid is then introduced into the coiled container e.g. using a hypodermic needle. A cover is placed over the outlet and finally the inlet is sealed. The inlet is of course situated such that it may be subsequently connected to a propellant source e.g. in a wall formed by the base.

Plastics or metal sheet may be used for sealing, preferably cellulose sheet, cellulose acetate sheet, polyvinyl chloride sheet, and also aluminium sheet or foil. The sheets must not be too thick that they readily tear under a slight pressure as the holder is placed over the valve of a propellant dispenser

and accordingly the upper end of the valve stem may enter a suitable recess in the holder base without the valve of the propellant container being opened in the insertion operation. A much greater pressure has to be applied to open the valve. Sheet or foil having a thickness of about 40 to 100 μ , especially that made from pure cellulose, is particularly suitable for the sealing.

The propellant source is preferably pressurized propellant dispenser provided with a dosing valve of known design. Particularly suitable for this purpose is one of the valves described in the above mentioned German Patent Specification No. 1 149 308, or a dosing valve marketed by Solfrene S.p.A., Corsico (Milan), Italy, under the designation MT/50-75-100. Where a dosing valve is employed, it is naturally a requirement that the single dose of propellant be sufficient to expel the entire dose of liquid from the holder according to the invention. On the other hand, it is possible to use arrangements of holder and propellant container with dosing valves in which the charge carried in the propellant container is designed to satisfactorily empty a specific number of holders, e.g. a dozen. Each holder is used only once and then thrown away; the propellant container, however, remains in service until the prescribed number of holders have been emptied. It is moreover also possible to utilise compressed-air bulbs or flasks of the type used in the U.S. Patent Specification No. 2,519,555; furthermore, it is possible to use pressurized propellant dispensers not fitted with a dosing valve; in the latter case, however, it is extremely difficult to ensure that complete dispensing of the active substance liquid from the holder has occurred without an unnecessary excess of propellant having been discharged.

In the case of the dispensing of nasal or inhalation sprays using pressurised propellant dispenser charged e.g. with Feron (registered Trade Mark), the impeding of the propellant gas flow in the first turn, where a coiled container is used, results in a small amount of propellant gas being condensed, or even being dissolved, e.g. in oily solutions, emulsions or suspensions, in consequence of which it is possible to obtain a more finely divided spray of liquid from the dispenser.

Before use and after the outlet cover has been removed, the single-dose holder is placed on to the valve of the propellant dispenser without pressure being applied. The holder is introduced into the nose or mouth. The liquid is then sprayed or expelled by the holder being sharply pressed down on to the propellant dispenser. A new single-dose holder is used for each

application.

In addition to being used as throat and inhalation sprays, holders according to the invention may also be used for non-medical purposes, e.g. in tests in which it is required to deliver or spray out small but very accurately measured doses of the active substance, liquid, e.g. in lubrication tests with newly developed lubricating oils; in insecticidal tests, in which the aim is to determine the minimum effective dose for certain insects in an experimental chamber with employment of the very smallest amounts of new test substances; and in the case of other applications where the main requirement is the utmost accuracy in the dispensing of minute doses.

The invention is further illustrated with reference to the accompanying drawings:

Fig. 1: shows, partially in cross section, a first embodiment of the single-dose holder sealed at both ends;

Fig. 2: shows the same holder, partially in cross section mounted on the dosing valve of a propellant dispenser — known per se; the dosing valve in this drawing is shown in cross section and in the sealed or closed position;

Fig. 3: shows the same arrangement as in Fig. 2, but with the valve in the open position;

Fig. 4: shows a further embodiment of the holder partly in cross section; and

Fig. 5: shows a further preferred embodiment of the holder in longitudinal section.

The embodiment shown in Fig. 1 of the single-dose holder comprises a casing or housing 1 serving as the nose- or mouth-insertion-piece, a rounded base 2, which is screwed into the lower end of the casing 1 by means of the thread 3, a hose or tubing section 4 having three or more turns and preferably made of synthetic material, e.g. polyethylene, the lower open end of the said hose or tubing being inserted into a central aperture 5 of the base 2 and held, e.g. by collars 6 and 7, and the upper open end into the outlet orifice 8 of the casing 1. After insertion of the single dose of liquid to be administered, the outlet orifice 8 is sealed by a cover 11 fitting over the thickened top 10 of the casing 1 and clipping into the narrowed neck 9, the said cover being removed before application of the holder. In the lower open end of the base 2, a recess 12 is provided which is directly below and adjoining a hollow space 13 of smaller diameter than the recess 12, the base 2 being sealed across its lower inner face, after filling of the tubing 4, by a plastics or aluminium sheet 14. The middle portion of the tubing 4 is charged with the liquid dose 15 to be sprayed; the two end portions of the tubing, 4 however,

contain no liquid.

Fig. 2 and 3 show the holder with the base 2 on top of the dosing valve of a propellant dispenser 20, the design being such that in the position shown the valve stem 21 of the dosing valve has pierced the aluminium sheet 14, and penetrated with its upper end into the hollow space 13, the top end of the stem being thus directly in contact with the upper end face of the hollow space 13 in Fig. 1, the valve stem 21 remaining, however, by virtue of the pressure of the spring 22 against the valve spring cap 23, in the sealed position. The cover 11 has already been removed.

The dosing valve known per se comprises, besides the stem 21 and valve spring cap 23, the valve housing 24 the splayed out upper edge 25 of which locates on the edge 26 of the neck 27 of a propellant container 28, and the valve cap 30; which is rigidly connected with the upper part of the wall of the propellant container 28, e.g. by means of the thread 31, and which has a dome-shaped part 32 situated above the valve housing 24, the dome-shaped part 32 being provided with a central opening 33, through which extends the upper end of the valve stem 21, the latter having an axial bore or channel 34. Between the valve cap 30 and the neck 27 of the propellant container 28 is inserted a flexible sealing ring 35, whilst a further flexible sealing ring 36 seals off the valve housing 24 against the cap 30, this seal 36 pressing, with the valve in the closed position, tightly against the upper face of the annular flange 37 of the valve stem 21.

The compression spring 22 is located in the lower part 40 of the valve housing 24, this lower part 40 having a somewhat smaller diameter than the upper part 41 with its widened top edge 25, the lower part 40 being provided in its base with an inlet aperture 42 for propellant from the container 28. Below the flange 37, the valve stem 21 extends downwards to form a hollow cylindrical section 43, the interior bore 47 of which at the top is separated from the cylindrical bore 34 by a solid section 44. The flange 37 and the hollow cylindrical section 43 of the valve stem 21 slide with clearance inside the upper part 41 of the valve housing 24. The lower part 45 of the hollow cylindrical section 43 has a reduced diameter and extends into the valve spring cap 23 in the lower part 40 of the valve housing 24. Between the outside of the hollow cylindrical section 43 and the inside wall of the upper part 41 of the valve housing 24 there is formed an annular space 46, which constitutes the dosing space for the propellant. In the wall of the hollow cylindrical section 43 there is provided approximately level with the upper end of the cylindrical bore 47, a connecting

aperture 48 so as to provide a connection between the dosing space 46 and the interior of the valve spring cap 23 via the cylindrical bore 47. The bore 47, aperture 48 and the cavity in cap 23 serve to enlarge the volume of propellant available for a single spray operation. From the lower end of the bore 34 of the valve stem 21 there is arranged an aperture 49 which, in the closed position, is situated just above the sealing ring 36 so that, in this position, the bore 34 is connected with the atmosphere to ensure uniform pressure. This condition obtains, by virtue of the lateral slot 50 in the inside wall of the base 2, even when the dispenser is mounted as in Fig 2.

The end portion 45 of the valve stem 21 extends into the central cavity of the valve spring cap 23, and there is arranged a sealing ring 52 between the hollow cylindrical part 43 having the full diameter of the valve stem 21 and the upper edge of the valve spring cap 23. The sealing ring 52 has a greater diameter than both 43 and 21. In the closed or inoperative position of the dosing valve, the dosing space 46 is connected, via the annular space 53 existing between the valve spring cap 23 and the inside wall of the bottom part 40 of the valve housing with the interior space of the lower part 40 of the housing situated below the valve spring cap 23, and the aperture 42 in the base of the lower part of the valve housing, with the interior of the propellant container 28, whilst the flange 37 of the valve stem 21 is located against the sealing ring 36 thus preventing any escape of the gaseous propellant.

If, after the outlet opening has been directed on to the point to be treated, the valve stem is moved, with compression of the spring 22, into the valve housing, this movement being effected by a reasonable amount of pressure on the holder base 2, which can be applied, e.g. with two fingers whilst the dispenser 28 is held in the same hand, then the device is in the spraying position shown in Fig. 3. In this position, the sealing ring 52 becomes pressed into the necking part 55 between the upper part 41 of the valve housing and the lower part 40, with the result that no further propellant can flow from the inside of the container 28 into the dosing space 46. At the same time, the flange 37 has moved downwards from the sealing ring 36, and the aperture 49 moves to a position below this sealing ring so that, in this position, the dosing space 46 is connected, via the interspace between the flange 37 and the inside wall of the upper part 41 of the valve housing, and via the aperture 49, with the central channel 34, the propellant from the dosing space 46 being then able to expel the active substance liquid 15 from the turns of the tubing unit 4

and cause it to spray out from the orifice 8 of the holder head 10.

The emptied holder is now removed from the valve of the propellant dispenser, the valve stem 21 returns to its inoperative position (fig. 2), thus enabling a fresh dose of propellant to flow into the dosing space 46; after positioning of a new loaded holder, the process can then be repeated.

Fig. 4 shows a similar dispenser as illustrated in Figures 1 to 3, but the container 104 in this embodiment has a different design, this embodiment comprises two end zones 110 and 111 forming capillaries, and an enlarged central zone 112. This widened zone in Fig 4 is of distended form having approximately a rhombic longitudinal section; it can, however, also be oval or circular in longitudinal section.

The preferred embodiment shown in Fig. 85 of a single dose holder according to the invention comprises the casing 200 having a thinner upper end compared with the main part 201 of the casing 200, designed for insertion, e.g. into the nose, and a base part 202 which widens out downwards and is open at the base.

The upper straight end section 211 of the spiral-shaped storage element 204 is firstly inserted from below, through the recess 212 formed by the widened base part 202, into the outlet aperture 208 arranged on the longitudinal axis of the mainpart 201 of the casing 200, the set of coils 215 thus coming up at 209 against the wall of the casing interior 207. The lower straight end section 213 of the storage element 204 is pushed into the centrally arranged axial inlet channel 205 in the neck 214 of an internal plug member 206 which, by means of a thickened section 235 on the inside edge of the neck 214, is snapped into place over the internal projection 216 of the base part 202, the neck 214 thus sealing against the lower inside wall of the casing interior 207. The set of turns 215 is located on the upper end of the neck at 210.

Insertion of a single dose of the liquid to be sprayed is effected, with open end sections 211 and 213 of the storage element 204, by means of an injection syringe, the needle of which is inserted into the bore, of the upper end section 211. The top outlet opening 225 is sealed on storage by a cover 217, the lower open end of which is level with and surrounds the lower edge of the base part 202. On the outer bottom rim of the cover 217 is provided an annular projection 218. The lower opening 219 of the inlet channel 205 is sealed by the nipple 221 of an essentially conically shaped sealing member 220 designed with its bottom edge bent up to form a collar 222, this collar being provided on the inside of its upper open end with an annular thickening or rim 223, 130

which positively engages over the lower projecting rim 218 of the cover 217, thus firmly holding together the assembly formed by casing 200, cover 217 and sealing member 220. The upper central part 224 of the cover is pressed onto the top end 201 of the casing, thus tightly sealing the opening 225 of the outlet channel 208, and the nipple 221 firmly against the inner aperture 219 of the inlet channel 205 of the plug member 206, the result being that the upper and the lower apertures of the storage unit 204 are maintained hermetically sealed. The pockets of air present at both ends of the capillaries in the straight sections 211 and 213 impede a premature displacement of the amount of liquid inside the set of turns 215, and prevent separated threads of liquid forming in the capillary end sections as a result of shaking, and the possibility of liquid itself reaching the sealing elements 221 and 224. To put the device into operation, the sealing member 220 is firstly withdrawn downwards, and the valve stem of pressurised dispenser, or similar propellant source, inserted into the opening 219 of the inlet channel 205 in the neck 214 of the plug member 206; the cover 217 is then removed, whereupon a small amount of propellant suffices to eject in spray form the complete dose of liquid from the set of turns 215 and through the outlet channel 208 and, finally, through the opening 225.

WHAT WE CLAIM IS:

1. A single liquid dose holder comprising a liquid dose in a container having an inlet and an outlet, means for connecting the inlet to a propellant source and a removable or rupturable seal on the inlet, the holder being such that the liquid dose is held by capillarity in the container with a gas pocket between the said seal and the liquid dose to impede displacement of liquid from the container.
2. A holder according to claim 1 which also comprises a removable or rupturable seal on the outlet.
3. A holder according to claim 2 wherein the container at its inlet and its outlet ends is in the form of capillary tubes, there being gas pockets in both capillary ends to impede displacement of liquid dose from the container.
4. A holder according to any one of claims 1 to 3 wherein the container con-

tainer consists of tubing having at least one turn.

5. A holder according to claim 4 wherein the tubing has at least two turns.

6. A holder according to claim 4 or 5 60 wherein the container consists of a capillary tube.

7. A holder according to claim 6 wherein the container consists of a tube having an inside diameter of 0.8 to 1.5 mm. and the viscosity of the liquid dose is 10 to 50 centipoises at 20°C.

8. A holder according to any one of the preceding claims wherein the container is of polyethylene, polyamide, polytetrafluorethylene, glass or metal.

9. A holder according to any one of the preceding claims wherein the inlet seal is rupturable.

10. A holder according to claim 9 75 wherein the inlet seal is rupturable on attachment of the holder to a propellant container without the pressure required for this operation being sufficient to effect discharge of propellant from the propellant container into the holder.

11. A holder according to claim 10 wherein the inlet is sealed by a sheet or foil of cellulose, cellulose acetate, polyvinyl chloride or aluminium having a thickness of 85 40 to 100 μ .

12. A holder according to any one of claims 1 to 9 wherein the inlet is sealed by a conically shaped sealing member firmly and detachably secured over the inlet or in a recess in the inlet.

13. A holder according to any one of the preceding claims wherein the liquid dose weighs 20 to 100 mg.

14. A single liquid dose holder substantially as hereinbefore described with reference to Figures 1 to 3 of the accompanying drawings.

15. A single liquid dose holder substantially as hereinbefore described with reference to Figure 4 of the accompanying drawings.

16. A single liquid dose holder substantially as hereinbefore described with reference to Figure 5 of the accompanying drawings.

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Fig.1

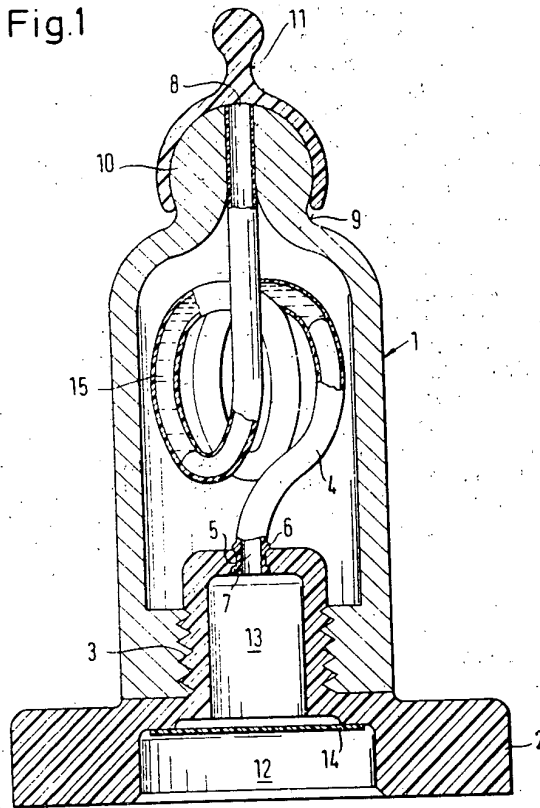
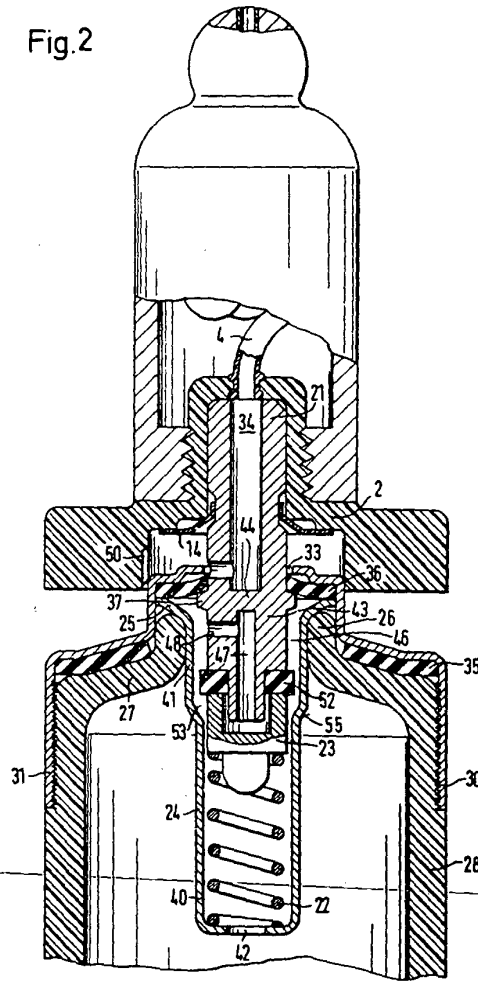


Fig.2



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COMPLETE SPECIFICATION

5 SHEETS

*This drawing is a reproduction of
the Original on a reduced scale
Sheet 3*

Fig.3

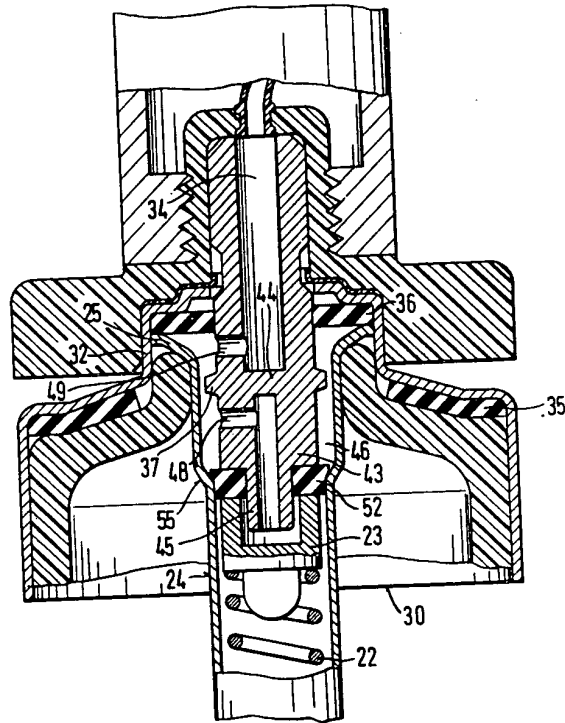
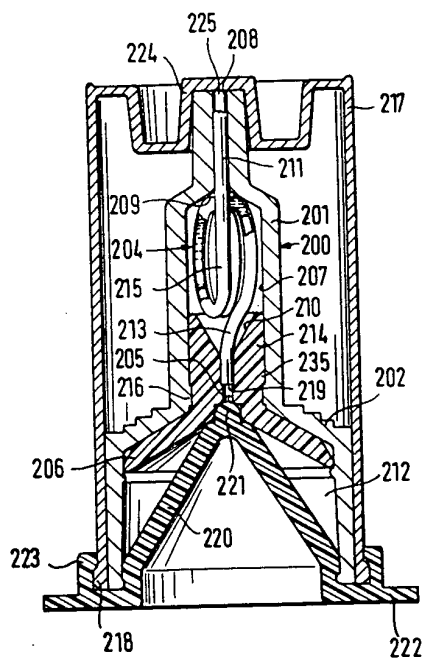


Fig.5



1380350

COMPLETE SPECIFICATION

5 SHEETS

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Sheet 4

Fig.4

